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CLINICAL RESEARCH STUDY

A Randomized, Controlled, Trial of Controlled Release Paroxetine in Fibromyalgia

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ABSTRACT

PURPOSE: We investigated the efficacy and tolerability of paroxetine controlled release, a selective serotonin reuptake inhibitor in fibromyalgia.

METHODS: After excluding patients with current major depression and anxiety disorders, 116 subjects with fibromyalgia were enrolled in a 12-week, randomized, double-blind, placebo-controlled, trial of paroxetine controlled release (12.5-62.5 mg/day). The primary outcome measure was proportion of responders as defined as a $\geq 25\%$ reduction in scores on the Fibromyalgia Impact Questionnaire (FIQ) from randomization to end of treatment. Secondary outcome measures included changes in FIQ scores, Clinical Global Impression –Improvement (CGI-I) and Severity (CGI-S) scores, Visual Analogue Scale for pain scores, number of tender points, and scores on the Sheehan Disability Scale (SDS).

RESULTS: Significantly more patients in paroxetine controlled release group (57%) showed a $\geq 25\%$ reduction in FIQ compared to placebo (33%) ($P=.016$). Paroxetine controlled release was significantly superior to placebo in reducing the FIQ total score ($P=.015$). The CGI-I ratings significantly favored the drug over placebo ($P<.005$). The improvements on other secondary outcome measures between the 2 groups were not statistically significant. Drowsiness, dry mouth, blurred vision, genital disorders, and anxiety were reported more frequently with paroxetine controlled release. The mean dose of paroxetine controlled release was 39.1 mg/day.

CONCLUSIONS: Paroxetine controlled release appears to be well-tolerated and improve the overall symptomatology in patients with fibromyalgia without current mood or anxiety disorders. However, its effect on pain measures seems to be less robust.

Fibromyalgia is characterized by chronic, widespread musculoskeletal pain and stiffness, in association with fatigue, sleep disturbances, and presence of tender points.[1-2] Altered pain processing, dysregulation of serotonin and norepinephrine systems, stress-response abnormalities, autonomic nervous system dysfunction, as well as psychosocial factors have been implicated in the pathophysiology of fibromyalgia.[3-6]

Meta-analyses of randomized, controlled trials have found that antidepressants are effective in fibromyalgia, although it is unclear whether this effect is independent of depression. [7-9] Five published controlled trials have examined the role of selective serotonin reuptake inhibitors in fibromyalgia; 3 involved fluoxetine[10-12] and 2 involved citalopram.[13,14] The results have been conflicting. In a well-designed 12-week study, Arnold et al[10] found that fluoxetine significantly improved scores on the Fibromyalgia Impact Questionnaire (FIQ) and Pain Questionnaire, but not the tender point or myalgic scores. In contrast, Wolfe et al[11] found no significant benefit of fluoxetine in a 6-week trial. A crossover study found both fluoxetine and amitriptyline had significant benefit compared to placebo and both were

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better when given together.[12] An 8-week trial with citalopram was negative,[13] while another study with citalopram over 16 weeks found significant improvement in depressive symptoms but no benefit on overall improvement.[14]

Three studies have examined the role of paroxetine in fibromyalgia. In an unpublished, 8-week trial from Belgium, paroxetine separated from placebo on the clinician rated, but not the patient rated, improvement scales.[15] A single-blind, 12-week trial from Italy, found that paroxetine was superior to placebo in improving tender point scores and ratings of improvement; however, this study did not define the primary efficacy measure.[16] Finally, a double-blind, triple crossover study found a combination of paroxetine and nabumetone to be significantly superior to nabumetone alone, but not to paroxetine alone, in reducing the total FIQ scores.[17] Although there is evidence of some benefit, sample size issues have limited interpretation of results from antidepressant trials. Recently, antidepressants acting on both serotonin and norepinephrine mechanisms have been hypothesized to have preferential benefit in fibromyalgia; however, the evidence is still emergent. While Phase II trials of duloxetine and milnacipran demonstrated evidence of efficacy,[18,19] a recently completed, large Phase III trial of milnacipran failed to reach statistical significance on pain, the primary efficacy measure.[20]

The objective of this study was to evaluate the efficacy and tolerability of paroxetine controlled release in the treatment of fibromyalgia.

CLINICAL SIGNIFICANCE

- Paroxetine controlled release appears to symptomatically benefit patients with fibromyalgia, including those who do not have clinical depression or anxiety.
- Although selective serotonin reuptake inhibitors may be appropriate therapeutic options in fibromyalgia, alternative or additional approaches to treat pain may be required.

METHODS

Overview and Design

This was a 12-week, randomized, two-site, double-blind, placebo-controlled study designed to assess the efficacy of paroxetine controlled release (12.5 to 62.5 mg/day) in fibromyalgia. The study was approved by the Institutional Review Boards of Duke University, NC and Thomas Jefferson University, Penn. The protocol was conducted under an Investigational New Drug (IND) obtained from the Food and Drug Administration. All subjects provided written informed consent prior to participation.

Subjects

Subjects were recruited through referrals and advertisements. Eligible subjects included men and women, 18-65 years of age, who fulfilled American College of Rheumatology diagnostic criteria for fibromyalgia.[1] Other inclusion criteria included a Visual Analogue Scale for pain score of ≥ 5 and a Beck Depression Inventory[21] score of ≤ 23 at screening and placebo lead-in visits. Eligible subjects were required to discontinue all prescription medications for fibromyalgia. Approved methods of contraception were required for women.

Exclusion criteria included inflammatory disease, unstable medical diseases, psychotic disorders, current depressive or anxiety disorders, substance abuse in the previous 12 months, history of hypersensitivity to paroxetine or paroxetine controlled release, involvement in workers compensation or related litigation, or pregnancy.

Concomitant medication exclusion included psychotropics, analgesics, muscle relaxants, steroids, and hypnotics, except over-the counter analgesics (acetoaminophen up to 4 grams/day, ibuprofen up to 1.2 gm/day) as rescue medications. A minimum 7-day washout was required for all antidepressants except fluoxetine (minimum 5-week washout). Concomitant medications such as antihypertensives that were not prescribed for fibromyalgia required a minimum of 4 weeks on a stable dose.

Outcome Measures

The primary outcome measure was response as defined by $\geq 25\%$ reduction on the Fibromyalgia Impact Questionnaire (FIQ) total score.[22] The FIQ is a 10-item, self-report instrument that measures multiple symptoms, functioning, and overall well-being. The scores range from 0 to 100. The FIQ has been found to have good reliability and validity in clinical trials.[23,24]

The secondary outcome measures included the change in FIQ Scores from randomization to end of treatment, a Clinical Global Impression-Improvement (CGI-I) score of 1 (very much better) or 2 (much better) at end of treatment, and a decrease of 1 point or more on the Clinical Global Impression (CGI-S) scores.[25] Other secondary measures included $\geq 25\%$ reduction in scores on the Visual Analogue Scale (VAS) for pain, and changes in number of tender points and scores on the Sheehan Disability Scale (SDS). The VAS is a 100-item self-report scale anchored by 'no pain' at one end and 'the worst pain I can imagine' at the other. The SDS[26] is a self-rated assessment of impairment in occupational, social, and family functioning. Tender points were examined using the protocol described by Wolfe et al.[1] The tender point count (TC) is the raw number of positive tender point scores elicited by palpation. The maximum TC can be 18. The tender point index (TI) is the sum of all 18 point scores. The maximum TI score can be 72.

Randomization and Blinding

The procedures followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[27] Randomization

(1:1) was determined by the Investigational Drug Service through a computer generated sequence. The trial staff obtained the randomization assignment over the phone at screening. The allocation sequence was concealed from the staff before and after assignment. The study drug and placebo were identical in appearance and taste. Adequacy of blind was tested after the study.

Study Procedures

The screening phase (Visit 1) included a review of medical history, the Mini International Neuropsychiatric Interview[28], a physical examination, recording of vital signs and concomitant medications, EKG, and laboratory tests. The Mini International Neuropsychiatric Interview yields diagnoses consistent with the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV).[29] Subjects were assessed for depression and anxiety using the Beck Depression Inventory (BDI)[21] and the Beck Anxiety Inventory (BAI).[30]

The screening visit was followed by a 1-week, single-blind, placebo run-in phase (Visit 2). Subjects who had a $\geq$ 25% reduction in FIQ scores at the end of the lead-in phase (placebo responders) were excluded. At visit 3, subjects were randomized to receive paroxetine controlled release or placebo. The starting dose was initiated on Day 1 and increased weekly to the maximum tolerated dose according to a forced titration schedule: Week 1: 12.5 mg/day, Week 2: 25 mg/day, Week 3: 37.5 mg/day, Week 4: 50 mg/day, Week 5-Week 12: 62.5 mg/day. Subjects were evaluated weekly for the first 4 weeks (visits 4-7) and every 2 weeks for the next 8 weeks (visits 8-11). After the final visit (week 12 or early termination), the study drug was tapered over 2 weeks. Adverse events were determined by the Systematic Assessment for Treatment Emergent Events-General Inquiry,[31] and measurements of vital signs and weight. Compliance was assessed by pill count.

Sample Size Calculations and Statistical Analysis

Power estimates based on the milnacipran trial[19] showed that a sample size of 120 was sufficient to detect a drug vs placebo difference in response of 60% vs 35% with 0.83 power and a between-group difference of 6 points in total FIQ score, with 80% power with an $\alpha < .05$.

An intent-to-treat analysis with last observation carried forward (ITT with LOCF) examining all randomized subjects and a completer analysis for all subjects who completed the study was performed. Changes in efficacy measures between the drug and placebo groups were examined using Analysis of Variance (ANOVA). Survival analysis using a Wilcoxon-rank sum test examined differences in the proportion of responders among the treatment groups over the study period. Safety analysis consisted of the descriptive analysis of adverse events, changes in vital signs and clinical laboratory assessments.

RESULTS

Subjects

983 subjects were screened over the phone, 180 subjects came in for an on-site screening visit, 124 subjects met the entry criteria and entered the placebo-run phase, and 116 were randomized to receive paroxetine controlled release or placebo. 30 (25.9%) subjects dropped out of the trial, 20 (34.4%) in the drug group and 10 (17.4%) in the placebo group. Figure 1 summarizes the subject disposition through the trial.

94% of subjects were women. There were no significant differences at baseline between the drug and placebo groups in terms of demographic and clinical characteristics (Table 1). The mean dose of paroxetine controlled release was 39.1 $\pm$ 8.6 mg/ day.

EFFICACY MEASURES

Primary Outcome

Survival analyses showed that significantly greater proportion of subjects in the drug group responded (56.8%) than in the placebo group (32.7%) (χ^2 (Breslow) = 15.75, P =.016). Fifteen (25.8%) of paroxetine controlled release versus 8 (13.7%) of placebo-treated subjects showed a $\geq$ 50% reduction in FIQ (χ^2 = 6.42, P =.08). The Kaplan-Meier Survival curves for the 2 groups are shown in Figure 2.

Secondary Outcome

As shown in Figure 3, ANOVA demonstrated a significant reduction in FIQ in the drug compared to the placebo group (F(1,113)=25.28, P=.015). The mean treatment difference in FIQ was −6.4 in favor of paroxetine controlled release (95% C.I.:−11.4 to +0.9, P<.05). Paired t tests showed that the between-group difference in FIQ reached statistical significance during weeks 6-12 (P<.05).

The between-group comparisons on subscale scores on the FIQ showed that paroxetine controlled release was superior to placebo on fatigue (P<.05), anxiety (P<.05), and days felt good (P<.05). There was a trend favoring paroxetine controlled release for pain (P=.07) and depression (P=.08). There were no significant differences between drug and placebo on other subscale scores. Consistent with the ITT analyses, completer analyses of change in total FIQ scores favored paroxetine controlled release over placebo (F= 7.22, P<.05). 25 (65.7%) of the drug group responded, compared to 16 (33.3%) in the placebo group (χ^2= 12.29, P<.01).

Improvements in CGI-I scores were significantly superior in the drug group compared to placebo (F=13.47, P < .005). Based on a CGI-I score of 1 or 2, 33 (56.8%) of subjects receiving paroxetine controlled release were considered responders, compared to 15 (25.8%) receiving placebo (χ^2 = 15.11, P<.01). Improvements in the CGI-S scores did not differ statistically between the 2 groups (P =.08).

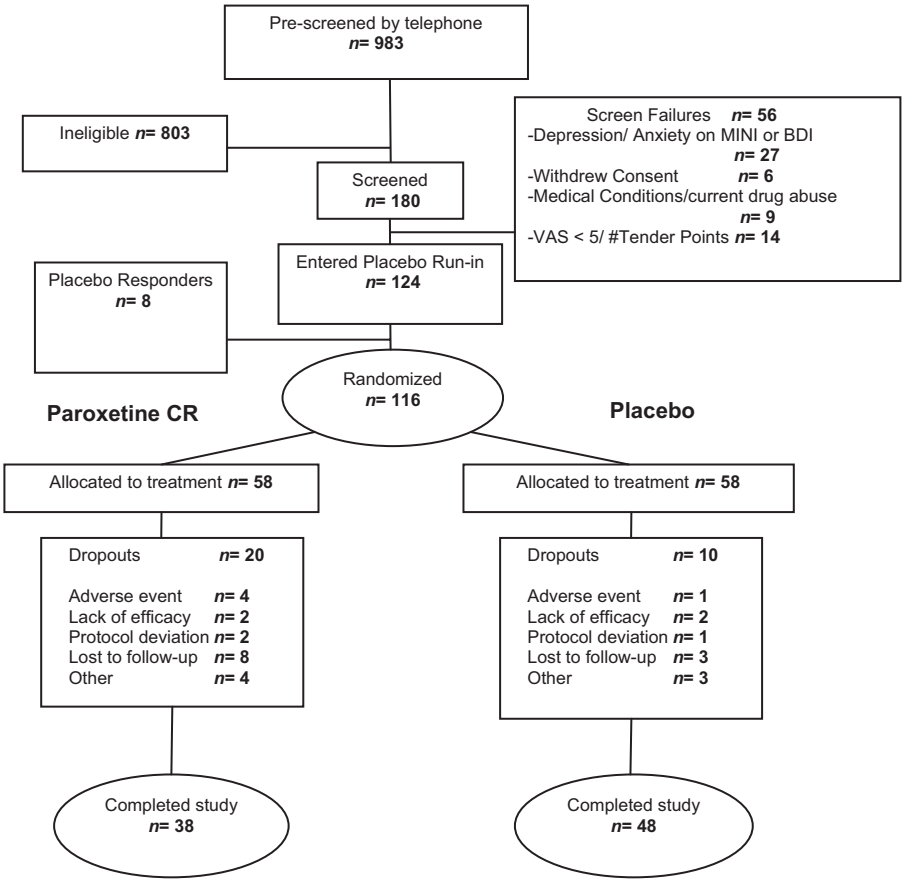

Figure 1 Study Disposition of subjects.

The change in VAS for pain scores did not significantly differ between the 2 groups (Paroxetine controlled release $= -12.2 \pm 18.5$, Placebo $= -8.8 \pm 16.6$, $P=.16$). There were no significant between-group differences in the proportion of subjects who showed a $\geq 25\%$ or a $\geq 50\%$ reduction in VAS from baseline to end of treatment. Comparisons between the drug and placebo groups on the tender point count, the tender point index, or the Sheehan Disability Scale scores did not yield any significant differences.

Table 1 Clinical Characteristics of subjects at randomization

	Paroxetine CR n=58	Placebo n=58
Gender		
Male	3 (5)	4 (7)
Female	55 (95)	54 (93)
Age (years)	47.9 (9.1)	49.1 (11.2)
Fibromyalgia Duration >5 years	28 (49)	31 (53)
Fibromyalgia Impact Questionnaire (0-100)	53.0 (8.9)	49.0 (12.2)
Visual Analog Scale for pain (0-100)	74.2 (22.7)	75.3 (19.8)
Beck Depression Inventory (0-63)	12.5 (5.9)	11.4 (6.4)
Beck Anxiety Inventory (0-63)	13.5 (9.7)	13.8 (9.9)
Tender Point Score (0-18)	17.2 (3.2)	16.9 (3.6)
Sheehan Disability Scale (0-30)	15.1 (9.7)	15.9 (6.1)
Clinical Global Impression Severity (0-7)	3.7 (0.8)	3.7(0.9)

Values for Gender and Fibromyalgia duration represent number of subjects (%). All other values represent means (standard deviation) of scores. All comparisons were not significant

Adverse Events

Any treatment-emergent adverse event was reported by 38 (65.5%) of the drug and 34 (58.6%) of the placebo groups. Adverse events were cited as the reason for study discon-

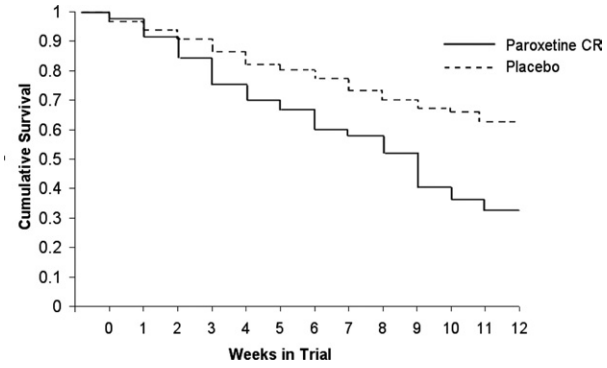

Figure 2 Kaplan-Meier survival curves for paroxetine CR and placebo groups. χ^2 [Breslow] = 15.75, df=1, $P=.016$. Response defined as $\geq 25\%$ reduction in Fibromyalgia Impact Questionnaire scores.

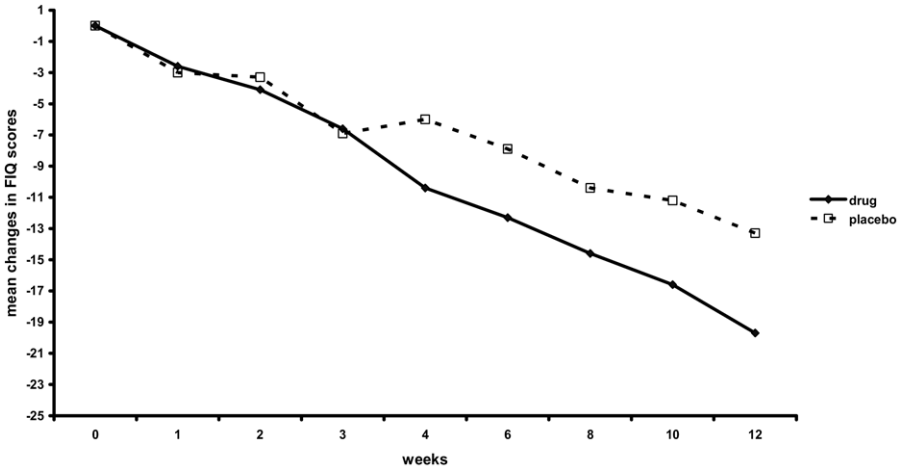

Figure 3 Mean changes in Fibromyalgia Impact Questionnaire scores (FIQ) from baseline to end of treatment in patients treated with paroxetine CR or placebo, LOCF. FIQ ranged from 0-100. ANOVA F(1,113) = 25.28, P=.015.

tinuation by 4 subjects receiving paroxetine controlled release and 1 subject receiving placebo. Two patients each in the paroxetine controlled release (renal infection, alcohol intoxication) and placebo (panic attack, fall) groups experienced a serious adverse event (SAE). Table 2 shows the treatment emergent adverse events reported by ≥5% of subjects.

As seen in Table 2, drowsiness, dry mouth, female genital disorders, ejaculatory problems, impotence, anxiety, and blurred vision were reported with ≥2 fold frequency with paroxetine controlled release than placebo. There were no significant changes in weight (lbs) between the 2 groups (Drug: baseline = 183 ± 42, week 12 = 185 ± 44; Placebo: baseline = 176 ± 46, week 12 = 175 ± 45, F = 1.78, P = .26). Concomitant medications were taken by 28% of the paroxetine controlled release and 37% of the placebo subjects (P = .31). There were no significant site specific differences on efficacy or safety endpoints.

Table 2 Treatment Emergent Adverse Events Occurring in 5% of subjects

	Paroxetine CR n=58	Placebo n=58
Drowsiness	15(26%)	4(7%)
Dry Mouth	21(36%)	5(9%)
Female Genital Disorders*	5(9%)	1(2%)
Ejaculatory Problems*	2(66%)	1(2%)
Impotence*	1(33%)	0(0%)
Headaches	10(31%)	15(26%)
Sleeplessness	10(17%)	5(9%)
Anxiety	8(14%)	4(7%)
Nausea	8(14%)	5(9%)
Diarrhea	5(9%)	7(12%)
Tremors	3 (5%)	2(3%)
Blurred Vision	3 (5%)	0 (0%)

*Corrected for gender. Values represent number of subjects followed by (%).

Success of Blinding

Only 7% of trials in medicine and 2% of trials in psychiatry report success of blinding.[32] 58% and 36% of subjects correctly guessed their drug and placebo assignment respectively (κ = 0.24, P = .28). Trial staff correctly guessed the drug assignment in 62% and placebo assignment in 55% of the subjects (κ= 0.17, P = .42).

DISCUSSION

Interpretation of Results

This is the largest randomized controlled trial of a selective serotonin reuptake inhibitor in fibromyalgia. The results indicate that paroxetine controlled release was superior to placebo on the primary outcome measure and some secondary outcome measures. The results were stronger in completer analysis indicating that subjects who remained on the drug appear to derive greater benefit. Because subjects with current mood or anxiety disorders were excluded, improvement in symptoms cannot be attributed to improvement in depressive or anxiety disorders. Studies have shown that a ≥25% reduction in FIQ scores may correspond to a ≥30% improvement in patients' ratings of benefit.[22] In other pain syndromes such as Rheumatoid Arthritis, a 20% threshold in improvement in the core parameters has been recommended as the primary efficacy measure.[33] Also, clinicians rated significantly more paroxetine controlled release-treated subjects as improved when compared to placebo. Therefore, the outcome criterion may indicate clinically meaningful improvement.

Paroxetine controlled release failed to separate from placebo on the pain or tender point scores. Among symptoms of fibromyalgia, tender points seem to be least likely to respond to antidepressants,[8] and symptom reduction may not be associated with tender point improvement.[34,35] There could be several reasons for the discrepancies in improvement on FIQ and pain scales. First, paroxetine controlled release may have less effect on pain compared to other

symptoms. Second, the paper and pencil scales may not be a sensitive enough instrument to capture changes in perception of pain. Real-time electronic diaries seem to be preferable to assess pain in fibromyalgia due to variability in pain reports.[36] Third, it is possible that higher doses of paroxetine controlled release might have had beneficial effects on pain. Pain perception appears to be modulated by both serotonin and norepinephrine influences,[37,38] and antidepressants with dual effects have been believed to be better to treat pain than selective serotonergic or noradrenergic agents.[18,39,40] Interestingly, higher doses of paroxetine (60 mg, approximately equivalent to 75 mg/day of paroxetine controlled release tablet) have been shown to decrease NE uptake by 43% at plasma concentrations of 200 ng/mL.[41] Finally, the FIQ measures report over 1 week, as opposed to the VAS which is a present state self report. Our results are consistent with those from a fluoxetine trial which found an improvement on the FIQ and Pain Questionnaires but not on tender point or myalgic scores.[10]

There were no major safety issues associated with the use of paroxetine controlled release. While dropouts due to adverse effects were higher in the drug compared to the placebo group, overall the drug was well tolerated. Consistent with clinical experience, drowsiness, dry mouth, and sexual dysfunction were reported more commonly with paroxetine controlled release than placebo.

Limitations

The two principal limitations of this study were the use of the FIQ as a single primary efficacy measure and brief study duration. Both the FIQ[10,42,43] and pain measures[18,44] have been used as primary endpoints in fibromyalgia trials. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended that 6 core outcome domains should be evaluated in chronic pain trials.[45] Consistent with these recommendations, composites of FIQ, pain, and subject ratings have been adopted as a primary efficacy measure in recent trials of sodium oxybate and milnacipran in fibromyalgia.[20,46] Because sustained benefit is difficult to demonstrate in short-term trials, recently the FDA has recommended a minimum of 24-week duration to demonstrate efficacy in fibromyalgia.

Generalizability issues deserve comment. The baseline characteristics indicated a moderately ill population typical of outpatient settings. However, the generalizability of these results could be affected by the fact that the study was conducted in only 2 sites, was short-term, and excluded patients with current depressive and anxiety disorders; this exclusion was needed to address the confounding effect of depression.

CONCLUSIONS

Our study demonstrates that paroxetine controlled release may symptomatically benefit patients with fibromyalgia, including those who do not have current clinical depression or anxiety. However, paroxetine controlled release did not demonstrate a statistically significant effect on pain-specific end-points. Further controlled studies, with longer duration and incorporating composites of core symptoms as efficacy measures are necessary to clarify the therapeutic role of selective serotonin reuptake inhibitors in fibromyalgia.

References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis & Rheumatism*. 1990;33:160-172.
2. Wolfe F, Aarflot T, Bruusgaard D, et al. Fibromyalgia and disability. Report of the Moss International Working Group on medico-legal aspects of chronic widespread musculoskeletal pain complaints and fibromyalgia. *Scandinavian Journal of Rheumatology*. 1995;24:112-118.
3. Offenbaecher M, Bondy B, de Jonge S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis & Rheumatism*. 1999;42:2482-2488.
4. Crofford LJ, Pillemer SR, Kalogeras KT, et al. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis & Rheumatism*. 1994;37:1583-1592.
5. Martinez-Lavin M and Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Seminars in Arthritis & Rheumatism*. 2000;29:197-199.
6. Goodnick PJ and Sandoval R. Psychotropic treatment of chronic fatigue syndrome and related disorders. *Journal of Clinical Psychiatry*. 1993;54:13-20.
7. Arnold LM, Keck PE Jr, and Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics*. 2000;41:104-113.
8. O'Malley PG, Balden E, Tomkins G, et al. Treatment of fibromyalgia with antidepressants: a meta-analysis. *Journal of General Internal Medicine*. 2000;15:659-666.
9. Versiani M, Ontiveros A, Mazzotti G, et al. Fluoxetine versus amitriptyline in the treatment of major depression with associated anxiety (anxious depression): a double-blind comparison. *International Clinical Psychopharmacology*. 1999;14:321-327.
10. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *American Journal of Medicine*. 2002;112:191-197.
11. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. *Scandinavian Journal of Rheumatology*. 1994;23:255-259.
12. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis & Rheumatism*. 1996;39:1852-1859.
13. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain*. 1995;61:445-449.
14. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia–a randomized, double-blind, placebo-controlled study. *European Journal of Pain*. 2000;4:27-35.
15. GlaxoSmithKline. Treatment of fibromyalgia: a randomized, double-blind, placebo-controlled study of paroxetine, a selective serotonin re-uptake inhibitor. Study ID 29060/433. 1995; Available at: http://ctr.gsk.co.uk/Summary/paroxetine/studylist.asp.
16. Giordano N, Geraci S, Santacroce C, et al. Efficacy and tolerability of paroxetine in patients with fibromyalgia syndrome: A single-blind study. *Current Therapeutic Research*. 1999;60:696-702.
17. Wetherhold EA, Carpenter DJ, Oakes R, et al. A randomized, double-blind, triple crossover study of the independent and combined efficacy of paroxetine and nabumetone in the treatment of fibromyalgia. Presented at the 40th annual NCDEU meeting, Boca Raton, Florida, 2000.

18. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis & Rheumatism*. 2004;50:2974-2984.
19. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. *Journal of Rheumatology.* 2005;32: 1975-1985.
20. Forest Laboratories Press Release. Forest Laboratories, Inc. and Cypress Bioscience, Inc. Announce Results of Phase III Study for Milnacipran as a Treatment for Fibromyalgia. October, 2005. Available at: http://www.frx.com/news/PressRelease.aspx?ID=762239.
21. Beck AT and Steer RA. *Beck Depression Inventory*. San Antonio, TX, Harcourt, Brace and Jovanovich.
22. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *Journal of Rheumatology.* 1991;18:728-733.
23. Goldenberg DL, Mossey CJ, Schmid CH. A model to assess severity and impact of fibromyalgia. *Journal of Rheumatology*. 1995;22:2313-2318.
24. Dunkl PR, Taylor AG, McConnell GG, et al. Responsiveness of fibromyalgia clinical trial outcome measures. *Journal of Rheumatology.* 2000;27:2683-2691.
25. Guy W. Early *Clinical Drug Evaluation Unit (ECDEU) assessment manual for psychopharmacology. Revised*. National Institute of Mental Health, NIMH Publication, Bethesda, MD. 1976, DHEW Publ No.(Adm) 76-338:217-222.
26. Sheehan DV. *Sheehan Disability Scale*. 1983, Washington, D.C., American Psychiatric Association.
27. Moher D, Schulz KF, Altman DG, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Annals of Internal Medicine.* 2001;134:657-662.
28. Sheehan DV, Lecrubier Y, et al. The validity of the Mini International Neuropsychiatric Interview (M.I.N.I.) according to the SCID-P and its reliability. *European Journal of Psychiatry.* 1997;12:232.
29. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (4th ed.).* 1994, Washington D.C., American Psychiatric Association.
30. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting & Clinical Psychology.* 1988;56:893-897.
31. Levine J and Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacology Bulletin*. 1986;22:343-381.
32. Fergusson D, Glass KC, Waring D, et al. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *BMJ*. 2004;328:432.
33. Felson DT, Anderson JJ, Lange ML, et al. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum.* 1998;41:1564-1570.
34. Jacobs JW, Geenen R, van der Heide A, et al. Are tender point scores assessed by manual palpation in fibromyalgia reliable? An investigation into the variance of tender point scores. *Scandinavian Journal of Rheumatology.* 1995;24:243-247.
35. Nicassio PM, Weisman MH, Schuman C, et al. The role of generalized pain and pain behavior in tender point scores in fibromyalgia. *Journal of Rheumatology*. 2000;27:1056-1062.
36. Harris RE, Williams DA, McLean SA, et al. Characterization and consequences of pain variability in individuals with fibromyalgia. *Arthritis & Rheumatism*. 2005;52:3670-3674.
37. Zhuo M and Gebhart GF. Inhibition of a cutaneous nociceptive reflex by a noxious visceral stimulus is mediated by spinal cholinergic and descending serotonergic systems in the rat. *Brain Research*. 1992;585: 7-18.
38. Willis WD and Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *Journal of Clinical Neurophysiology*. 1997;14:2-31.
39. Sawynok J, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *Journal of Psychiatry & Neuroscience*. 2001;26:21-22.
40. Littlejohn GO. Balanced treatments for fibromyalgia. *Arthritis & Rheumatism*. 2004;50:2725-2729.
41. Gilmor ML, Owens MJ, Nemeroff CB. Inhibition of norepinephrine uptake in patients with major depression treated with paroxetine. *American Journal of Psychiatry*. 2002;159:1702-1710.
42. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *American Journal of Medicine*. 1998;104:227-231.
43. Sim J and Adams N. Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. *Clinical Journal of Pain*. 2002;18:324-336.
44. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis & Rheumatism*. 2005;52:1264-1273.
45. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005; 113:9-19.
46. Russell JI, Bennett RM, Michalek JE, et al. *A Randomized, Double-Blind, Placebo-Controlled Trial of Sodium Oxybate in Fibromyalgia Syndrome [FIBROMYALGIA].* American College of Rheumatology 70th Annual Scientific Meeting San Diego, CA, USA, 2005.